THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

JANUARY, 1964

ORIGINAL ARTICLES

THE MALIGNANT TRANSFORMATION OF FIBROUS DYSPLASIA

By David T. Schwartz, M.D.

AND

Meyer Alpert, M.D.
ASSISTANT PROFESSOR OF RADIOLOGY

(From the Radiological Service of the Presbyterian Hospital, New York, New York, and the Department of Radiology, College of Physicians and Surgeons, Columbia University, New York, New York)

In the 24 years since its original description by Lichtenstein[54] and Lichtenstein and Jaffe[55], the concept of fibrous dysplasia as a distinct entity has been generally accepted. There has been controversy, however, regarding its malignant potential. Lichtenstein[54], Coley and Stewart[14] and others (Daves and Yardley[20], Pisanni and Caprotti[69]) have doubted the sarcomatous transformation of fibrous dysplasia. Dahlin[18] and Tanner, Dahlin and Childs[85] found no examples of malignant change in this lesion without previous irradiation. To gather additional data on this problem, we have reviewed the world literature and our own experience at the Columbia-Presbyterian Medical Center. A total of 26 adequately documented examples of sarcomatous degeneration of fibrous dysplasia has been reported. In addition, there were 2 such cases in the records of the Presbyterian Hospital.

In this paper we shall evaluate the malignant potential of fibrous dysplasia by a critical analysis of these cases, assess the role of radiotherapy in the induction of these tumors, and estimate the frequency of malignant change.

Case Reports. CASE 1. A 15-year-old white boy was first seen at the Columbia-Presbyterian Medical Center on January 9, 1939, complaining of a mandibular swelling of 2 years' duration. At the onset of symptoms in 1937, a dentist was consulted, and he made the diagnosis of a cyst in the left side of the mandible. He then extracted the left lower first molar and curetted the lesion. When the histologic sections were interpreted as osteitis fibrosa cystica, Roentgen-ray therapy was begun. A total of ten treatments was given at another hospital, but the dose is not known. On physical examination at the Presbyterian Hospital, there was a hard, nontender mass overlying the body of the left side of the mandible. No nodes were palpable in the neck, and the remainder of the examination was unremarkable. A radiological survey of the ribs and long bones was normal. The serum calcium, phosphorus and alkaline phosphatase likewise were normal. On February 1, 1939, an open biopsy of the left side of the mandible was performed. A 7 cm. tumor was seen to involve the entire left side of the mandible, which was composed of both soft tissue and bone, with areas of cystic degeneration. The pathological diagnosis was again osteitis fibrosa cystica. There

was no evidence of malignancy on these sections. Instead of a second curettage, a second course of radiotherapy was given. Using the 200 K.V.P. beam (1 mm. Cu and 1.25 mm. Al filtration) and a 50 cm. T.S.D., a dose of 1600r was delivered to the center of the tumor in 10 days. No immediate change in the size of the lesion was noted.

In the interval from 1939 to 1945, there was only slight enlargement of the left mandible. He was seen in September, 1945, at the Presbyterian Hospital because of a left mandibular osteomyelitis following a dental extraction. The serum calcium, phosphorus and alkaline phosphatase remained at normal levels. After treatment with sulfadiazine, a partial resection of the mandible was carried out. The bulk of the lesion was removed anteriorly and posteriorly, but its superior portion could not be excised. Grossly, the specimen was exceedingly friable, and microscopic examination demonstrated the presence of a fibrosarcoma. Roentgenograms of the chest in November, 1945, showed no metastases. On December 4, 1945, a third course of radiotherapy was started, delivering 2700r to the center of the tumor in 40 days.

Eleven months later, however, the malignancy recurred, and he developed a buccal fistula. Electrocautery was employed to remove a portion of the tumor extending to the palate. From June 13 through June 26, 1946, a fourth course of radiotherapy was given, with an exposure dose in the center of the tumor of approximately 1800r.

Within 3 months, however, there was a recurrence, with intra-oral ulceration. In September, 1946, a left hemi-mandibulectomy was performed, but 3 months later the tumor recurred in the upper gingiva. In January, 1947, this gingival mass was resected en bloc. The surgical specimen showed fibrosarcoma of bone. Despite five local excisions in 1947, the tumor continued to recur. Terminally the patient developed postprandial vomiting and headaches, as a result of invasion of the sphenoid bone and intracranial extension. Roentgenograms of the chest, however, showed no pulmonary metastases. He died at home on December 8, 1947. There was no necropsy.

COMMENT. According to the modern classification of bone lesions, the histologic sections of the February 1, 1939, biopsy specimen showed the characteristic features of fibrous dysplasia. The period between the onset of the fibrous dysplasia and the onset of the sarcoma was 8 years. The patient received two courses of radiotherapy, one 8 and one 6 years prior to the development of the malignancy. Although the dose of

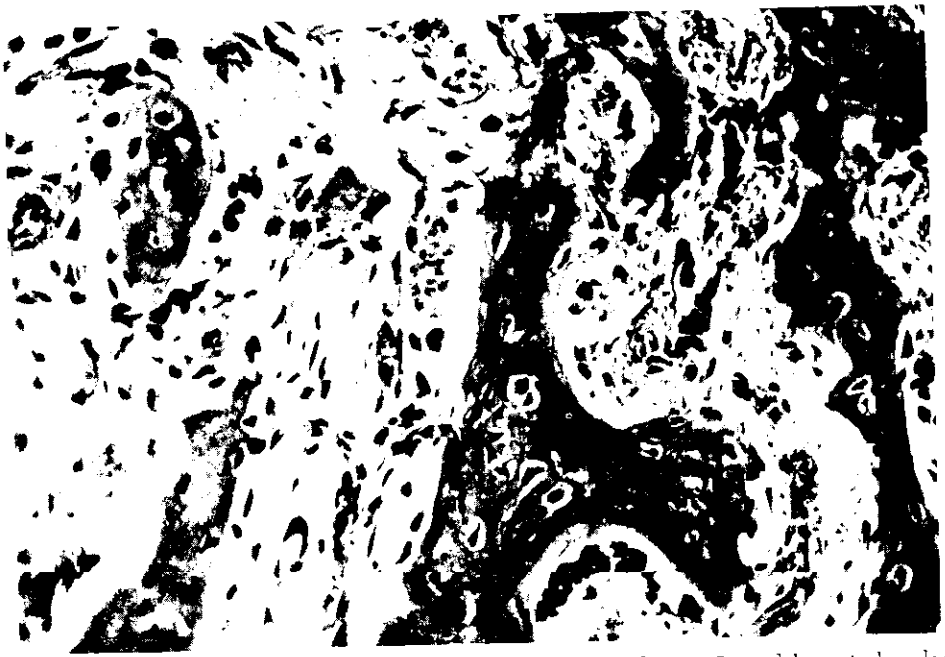

Fig. 1.—Case 1. Histologic section of mandibular fibrous dysplasia. Curved bone trabeculae are separated by loose, fibrous connective tissue.

Fig. 2.—Case 1. H

the first course
second course th
sion was given
days. The possib
considered that
tion played a r
transformation.
cal intervention
It did not show
to radiotherapy
caused death w

CASE 2. An 11-
examined at the
ical Center on O
a painless swellin
region of one ye
the right zygom
formed at another
report had been
examination revea
of the right side
involving the fr
and mandible. F
rosis and thicke
No other signifi
noted. The seru
alkaline phosph
of external Roe

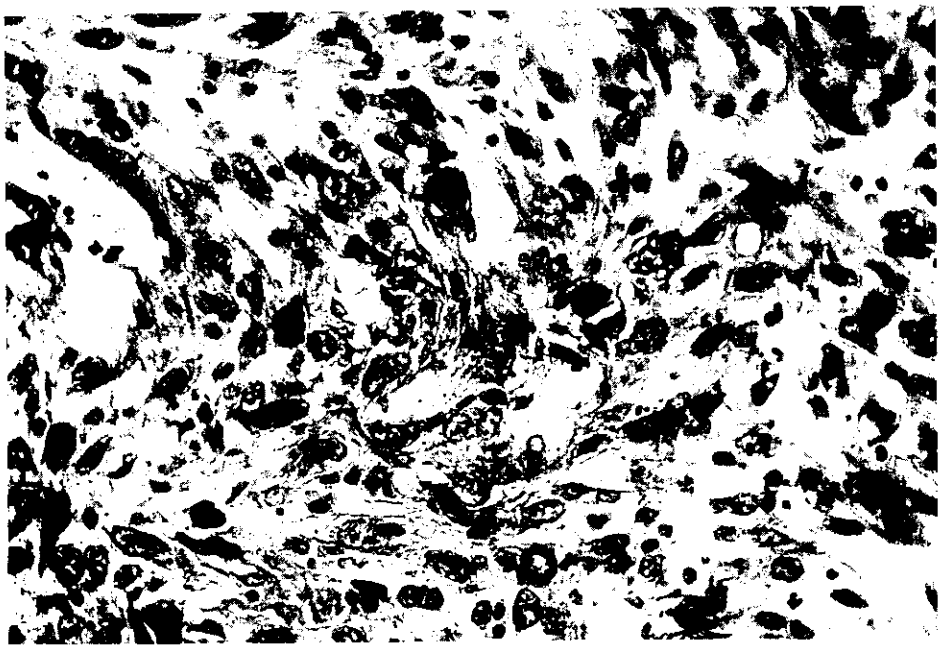

Fig. 2.—Case 1. Histologic section of fibrosarcoma engrafted upon fibrous dysplasia. The cells have a frankly malignant appearance.

the first course is not known, in the second course the fibrous dysplasia lesion was given a total of 1600 r in 10 days. The possibility must therefore be considered that the Roentgen-irradiation played a role in the sarcomatous transformation. Despite multiple surgical interventions, the tumor recurred. It did not show a favorable response to radiotherapy, and local extension caused death within 2 years.

CASE 2. An 11-year-old white girl was first examined at the Columbia-Presbyterian Medical Center on October 7, 1947, because of a painless swelling in the right infra-orbital region of one year's duration. A biopsy of the right zygoma had been recently performed at another hospital, and the pathologic report had been fibrous dysplasia. Physical examination revealed a striking prominence of the right side of the head and of the face, involving the frontal bone, zygoma, maxilla and mandible. Roentgenograms showed sclerosis and thickening of these bones (Fig. 3). No other significant symptoms or signs were noted. The serum calcium, phosphorus and alkaline phosphatase were normal. A course of external Roentgen therapy was begun on October 24, 1947, using a beam generated at 200 K.V.P. (0.5 mm. Cu and 1.25 mm. Al filtration), with a 50 cm. T.S.D. The dose at the center of the tumor was 1500r in 27 days. From 1947 to the beginning of 1951, there was no change in the size of the lesions. In April, 1951, she came to the hospital complaining of throbbing in the right side of the face. A second course of radiotherapy was started on April 26, with the same Roentgen-ray beam factors as described previously. The dose at the center of the lesion was 1600r in 14 days. The patient was asymptomatic for the next 4 years. In 1955, an attempt was made to correct the asymmetry of her face by removing some of the sclerotic bone from the right temporal fossa and zygoma. Four months later the abnormal bone arising from the right maxilla and mandible was resected. The histologic diagnosis of the excised material was fibrous dysplasia. On July 18, 1960, she returned to the hospital with a history of progressive enlargement of the right side of the face of one year's duration. More recently she noticed an intra-oral tumor and a spontaneous exfoliation of the right upper third molar. Physical examination disclosed a 4 cm. mass fixed to the posterior alveolar ridge. Intra-oral roentgenograms showed a diffuse lytic lesion in the right posterior maxilla. A biopsy of this tumor showed a bone

Fig. 3.—Case 2. Frontal radiograph of skull showing sclerosis of the right orbit, greater wing of sphenoid, maxilla and frontal bone due to fibrous dysplasia.

Fig. 4.—Ca

Fig. 5.—Case 2. There is an anap

sarcoma, but the pathologists could not determine whether it was a fibrosarcoma or an osteogenic sarcoma. The serum calcium and phosphorus remained normal, but the alkaline phosphatase was elevated to 18 King-Armstrong units. On August 2, 1960, the right external carotid artery was ligated, and 9 days later a right radical maxillectomy was performed. Except for a small residue in the pterygoid fossa, the tumor was completely extirpated. Histologically the specimen was interpreted as a fibrosarcoma. There was no evidence of recurrence until November 28, 1960, when she complained of a right-sided deafness and an intra-oral mass. A biopsy was reported as fibrosarcoma, and a subtotal right mandibulectomy was performed. The right external carotid artery was ligated during this procedure. Once again a small portion of the tumor in the pterygoid region could not be resected. To restrain its growth, a third course of radiotherapy was given, using the 22 Mev betatron. Five thousand roentgens were delivered to the center of the tumor in 33 days, the last treatment having been given on January 29, 1961. By May, 1961, however, there was a large recurrent tumor in the right pterygoid region. This mass was treated by local resection, using the electrocoagulator. For the first time, in June, 1961, roentgenograms of the chest demonstrated the presence of pulmonary metastases. She also had a tender nodule over the right anterior thorax, which corresponded to a radiographically demonstrable rib metastasis. In June and July of 1961 an intra-orally recurrent tumor was resected locally, but within one month it again filled the entire oropharynx. The patient was given a regional infusion of 282 mg. of methotrexate into the left external carotid artery over a 3-week period, ending August 14. The right external carotid artery could not be used for the infusion because it had been ligated previously. At the completion of the chemotherapy, her white blood cell count had fallen from a previously normal level to 150 per cmm., the platelets had fallen to 24,000 per cmm., and her temperature had risen to 104° F. During the last 2 days of this treatment she was moribund. She died on August 15, 1961.

NECROPSY FINDINGS. The base of the skull was markedly thickened, to a maximum of 2.5 cm. Histologically, the normal bone was replaced by areas of fibrous dysplasia. The pharynx was filled with a tumor extending from the sphenoid to the base of the tongue.

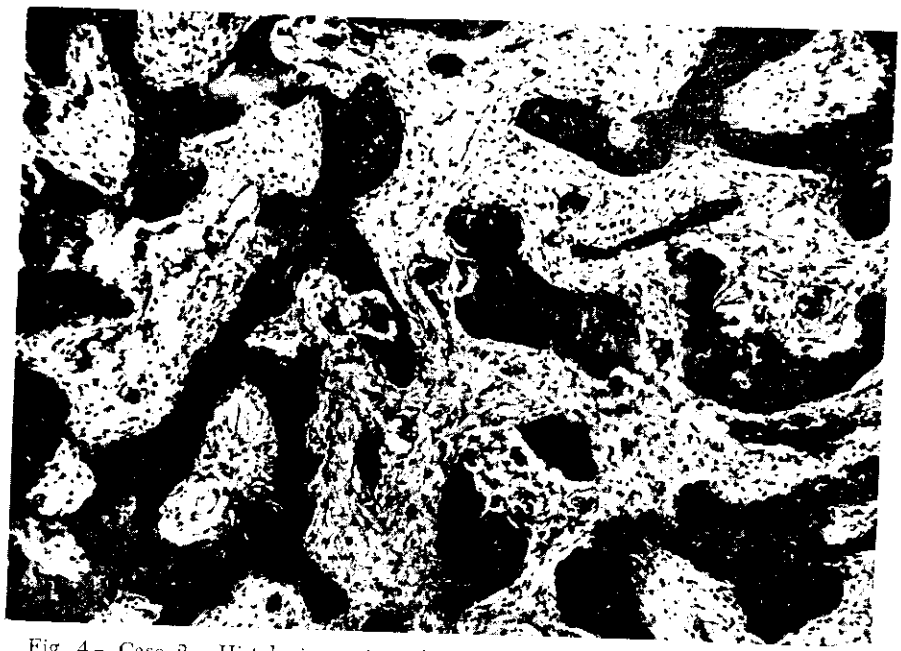

Fig. 4.—Case 2. Histologic section of maxillary fibrous dysplasia. The osseous trabeculae are thicker than in Case 1.

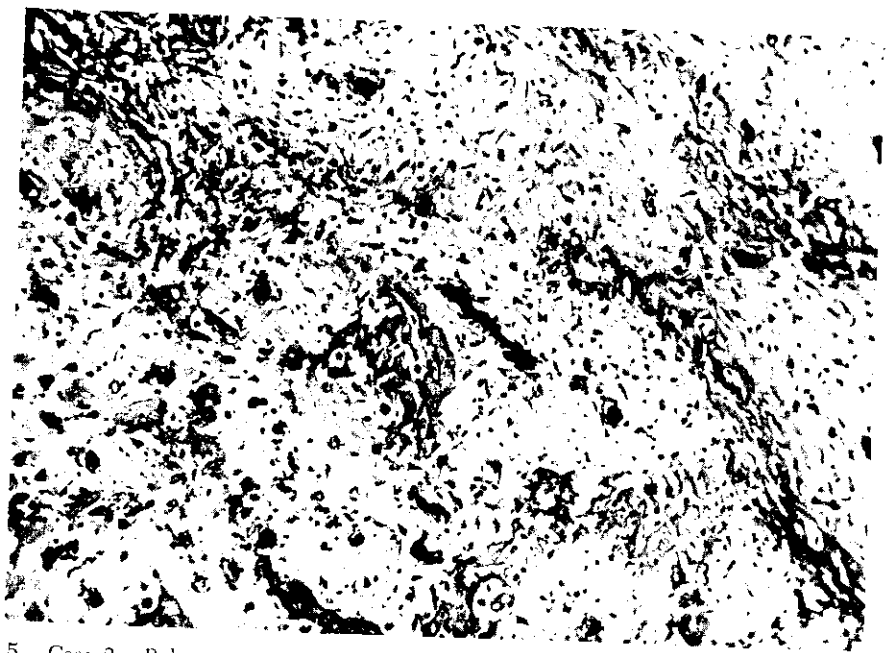

Fig. 5.—Case 2. Pulmonary metastasis of osteogenic sarcoma secondary to fibrous dysplasia. There is an anarchic array of abundant osteoid, a few poorly formed bone trabeculae and some fibrous tissue.

essentially fibrosarcomatous in nature, without osteoid or bone formation. There was a metastasis to an upper cervical lymph node. Sarcomatous masses involved the right third, fourth and fifth ribs and the sternum, invading the adjacent anterior mediastinum and lung. Several metastatic lesions were present in the right lower lobe, and these showed osteoid and bone formation on histologic examination. Confluent bronchopneumonia was present in both lower lobes.

COMMENT. The total tumor dose of 3100r delivered to the fibrous dysplasia lesion may have been a factor in the genesis of the malignancy (1500r T.D. in 27 days, 8 years prior to the sarcoma, and 1600r T.D. in 14 days, 4 years prior to the sarcoma). The lag between the onset of the fibrous dysplasia and the sarcoma was 14 years. Because of pterygoid fossa involvement, complete surgical extirpation of the osteogenic sarcoma was difficult, and it recurred repeatedly. Neither radiotherapy nor chemotherapy favorably influenced the clinical course of the tumor.

The necropsy findings are of interest, since there has been only one other case published with a necropsy (Jager[45]). While the histologic appearance of the primary tumor in this patient was that of a fibrosarcoma, the production of osteoid and bone in its metastases established it as an osteogenic sarcoma. The metastases that were demonstrated in the lymph nodes and bone are uncommon in osteogenic sarcoma.

Review of the Literature. When the authors began a search of the literature, it became clear that fibrous dysplasia was being indexed in the bibliographic periodicals under several synonyms, and these are listed in Table 1. It is unfortunate that the Index Medicus does not have a listing for the term "fibrous dysplasia."

We collected all the cases in the literature which were purportedly sarcomas secondary to fibrous dysplasia. In the very beginning we were able to exclude four papers (Belloni[7], Cabitza[9], Cahan *et al.*[10], Price[74]) since they did not contain any original cases. One of Jaffe's cases[40,41] had been reported previously by Sutro[51], Kragh, Dahlin and Erich's[52] 2 cases and Tanner, Dahlin and Childs' fourth case[53] had been previously published by Sabanas *et al.*[76]; Snapper's case[81–83] had been previously discussed by Parisel[66]. Leeds and Seaman[33] made reference to our second case.

TABLE 1. SYNONYMS FOR FIBROUS DYSPLASIA IN THE LITERATURE

Year	*Author*	*Term*
1933	Kienbock[35]	Cystofibromatose
1937	McCune and Bruch[1]	Osteodystrophia fibrosa
1937	Albright *et al.*[2]	Osteitis fibrosa disseminata
1938	Lichtenstein[36]	Polyostotic fibrous dysplasia
1940	Uehlinger[87]	Osteofibrosis deformans juvenilis
1956	Ferrero[29]	Osteofibromatose kistique
1957	Cottone[17]	Morbo di Jaffe-Lichtenstein

On careful study of the remaining reports, however, many cases had to be rejected since there was a reasonable doubt regarding the diagnosis of either the fibrous dysplasia or the sarcoma. In order to be consistent in accepting or rejecting reported cases, we formulated the following rules:

(1) A monostotic fibrous dysplasia lesion had to be histologically confirmed since we could not rely on only the clinical and Roentgen features.

(2) The diagnosis of polyostotic fibrous dysplasia, however, was ac-

cepted if there were characteristic clinical and Roentgen features.

(3) The diagnosis of sarcoma had to be confirmed histologically. One exception (Wanke[60]) was permitted, since the evidence for malignant degeneration and metastatic spread was unequivocal.

(4) A borderline group of cases was established (Table 3) for those instances where the diagnosis of either the fibrous dysplasia or the sarcoma was deemed only probable. These data were not used in the detailed analysis of the clinical findings.

(5) Cases were rejected outright when the data were grossly inadequate, or when the first three criteria were clearly not fulfilled. (Six cases (Elmslie[24], Haberer[32], Katz[47], Knaggs[50], Martens[61], Pick[65], Platt[70]) were excluded because they did not meet these criteria.)

With the 2 patients from the Presbyterian Hospital, there were 28 cases fullfilling our criteria. Fourteen had monostotic dysplasia, and 14 had polyostotic lesions. With only one exception (Portis[71]), the sarcoma developed in only one bone, and in all instances the affected bone was the seat of fibrous dysplasia. Of the 28 patients, 18 developed osteogenic sarcomas, 7 fibrosarcomas, 2 chondrosarcomas and one giant cell sarcoma (? osteogenic sarcoma). The salient features of these cases are summarized in Table 2.

CLINICAL FINDINGS. The age of onset of fibrous dysplasia in the 28 patients varied from 4 to 39 years, the mean being 16 years. The age of onset of sarcoma ranged from 8 to 61, the mean being 32 years. The lag between the development of the fibrous dysplasia and the sarcoma varied from a minimum of 2 years to a maximum of 30 years, the mean being 13.5 years. There was an equal number of males and females.

It was interesting to compare the clinical features of the patients who developed sarcoma after monostotic fibrous dysplasia with those of patients who developed the sarcoma after polyostotic fibrous dysplasia. Patients with monostotic fibrous dysplasia had the same age of onset as patients with polyostotic fibrous dysplasia. However, the lag before the development of the sarcoma was 15 years in the case of monostotic fibrous dysplasia and only 11.5 years in the polyostotic variety (Table 4). (This difference in the lag period was not statistically significant.) Among the cases of polyostotic fibrous dysplasia with subsequent sarcomatous change, the male:female ratio was 1:2, but it was approximately 2:1 in cases of monostotic fibrous dysplasia undergoing sarcomatous change ($P = 0.05$). Four of the polyostotic cases had Albright's syndrome.

IRRADIATED VERSUS NONIRRADIATED PATIENTS. In the 11 cases in which radiotherapy was given prior to the development of a sarcoma, the age of onset, sex distribution, lag period and prognosis were not significantly different from the 16 patients who did not receive radiotherapy prior to the development of their sarcoma. The proportion of osteogenic sarcoma to fibrosarcoma was similar in both groups of patients.

DISTRIBUTION OF THE SARCOMA IN THE SKELETON. The distribution of the sarcoma in the skeleton is represented in Fig. 6. Because cranio-facial fibrous dysplasia uncommonly affects just one facial bone, for purposes of this study, we have considered cranio-facial fibrous dysplasia as a monostotic form. The cranio-facial area was the site of the sarcoma in 10 of the 28 patients, and in 8 of the 10 the facial bones were involved. The next most frequent sites were the humerus, pelvis, tibia and fibula. The distribution of the sarcomas paralleled the distribution of the fibrous dysplasia. However, the distribution of the lesions of fibrous dysplasia differed among patients with the monostotic form as compared to those with polyostotic form. The most com-

TABLE 2.L. 28 ACCEPTABLE CASES OF SARCOMA FOLLOWING FIBROUS DYSPLASIA

			Fibrous Dysplasia Data				
Year	*Author*	*Sex*	*Age of onset*	*Bones affected*	*Symptoms*	*Treatment*	*Comments*
1927	Wanke[76]	F	7	Maxilla	Swelling, exopthalmos	Surgical exploration	
1928	Fromme[20]	M	38	Humerus	Pathological fracture	None	
1945	Coley and Stewart[13]	F	?	Ribs, pelvis, femur skull	None	None	
		M	?	Pubis, femur, tibia	?	None	Alk phos. elevated with sarcoma.
1949	Belloni and Zanetti[6]	F	16	Femur, hemipelvis	Heaviness in leg	Radiotherapy, tumor dose, 6,000–7,000 r, age 16	
1949	Snapper[61, 5]	F	7	Femurs, humerus	Precocious puberty, path. fractures, mental deficiency	Calcium injections, ultra-violet	Albright's syndrome
1950	Dustin and Ley[9]	F	7	Femurs, tibia, humerus, skull, hands, pelvis	Path. fractures, premature sexual development, pain in thigh	Radiotherapy, tumor dose, 1,600 r 8 mos.	Albright's syndrome, hypercalcemia
1951	Sutro[71]	M	25	Tibia, fibula, femur	Mass in leg	None	
1951	Cabitza[7]	M	36	Tibia, metatarsal	Pain on walking	Oper. interv. at both sites, with implantation of bone chips	
1955	Hall, Bersack, and Vitolo[24]	M	32	Tibia	Tenderness	Surgical exploration	
1955	Perkinson and Higinbotham[46]	M	14	Rib, skull, hemipelvis	Leg shortness, pain, difficulty walking, deafness	Radiotherapy, tumor dose, 2,370 r, in 31 days	Elevated alk phos. with onset of sarcoma
1956	Hobbs, Fischer and Beck[27]	M	20	Skull	?	None	
1956	Portis[47, 48]	F	?	Spine, scapula, humerus, radius	None	None	? multicentric sarcoma
1956	Sabanas *et al.*[57]	F	6	Maxilla	Swelling	Radiotherapy, ? dose	
1956	Trubnikov[70]	M	39	Femur	Pain	Surgical excision with implantation of bone chips	
1957	Parrini[45]	F	6	Maxilla, mandible, radius, ulna, hand, calvarium	Precocious puberty	Local resection (calvarium), age 8	Albright's syndrome
1958	Lobst[32]	F	7	Femur	?	?	

1956	Sabanas *et al.*[76]	F	6	Maxilla	Swelling	Radiotherapy, ? dose	
1956	Trubnikov[86]	M	39	Femur	Pain	Surgical excision with implantation of bone chips	
1957	Parrini[65]	F	6	Maxilla, mandible, radius, ulna, hand, calvarium	Precocious puberty	Local resection (calvarium), age 8	Albright's syndrome
1958	Jaffe[42]	F	7	Femur	?	?	
1958	Vakhurkina[85]	M	30	Left lower leg	Pain		
1961	Tanner, Dahlin and Childs[81]	M	10	Maxilla	?	Radiotherapy, skin dose 8638 r, age 7 years	
		M	8	Maxilla, mandible	?	Radiotherapy, skin dose 6070 r, in 11 years	
		M	22	Mandible	?	Radiotherapy, 750 r in 10 days	
1962	Harris, Dudley and Barry[31] case 13	M	4	70% of skeleton	?	Radiotherapy, (T.D. 1000–1500 r in 6 mo.), age 6	
	case 25	F	18	20% of skeleton	limp	Radium, 11,300 mg.-hr. in 7 mo., age 27	
1962	Kieh, DePrez and Harris[48]	F	37	Femur, pelvis, skull	?	?	
1962	Sethi, Clinic and Tuttle[80]	F	?	Rib	None	None	
1962	Jager[35]	F	12	Maxilla, clavicle, ribs, spine, radius, ulna, metacarpal, iliacs, femur, tibia	Unilateral pigmentation	None	Albright's syndrome, first report with necropsy
1963	Schwartz	M	13	Mandible	Swelling	Radiotherapy, at least 1000 r; curettage	
		F	10	Cranio-facial	Swelling	Radiotherapy, tumor dose, 3,000 r at age 16–20; curettage	Alk. phos. elevated with sarcoma

*On review by the Armed Forces Institute of Pathology, the original benign lesion was considered to be an unclassified fibroplasia. The omission of the Portis case is therefore justified.

TABLE 2B.—28 ACCEPTABLE CASES OF SARCOMAS FOLLOWING FIBROUS DYSPLASIA

	Sarcoma Data					Course			
Author	*Age of onset*	*Histologic type*	*Bone affected*	*Symptoms*	*Treatment*	*Length of follow-up (yr.)*	*Local recurrence*	*Metast.*	*Status*
Wanke[90]	37	"Spindle-cell"	Maxilla	Progressive swelling after tooth extraction	Heminandibulectomy	0	?	?	?
Fromme[29]	43	Osteogenic	Humerus	Pain	Disarticulation	5 1/2	+	+	Dead
Coley[14]	42	Osteogenic	Scapula	Pain, swelling, limitation of motion, weight loss	Radium (2800 mg.-hrs.) in 5 days; and R.T.? dose	13	+	+	Dead
	34	Giant-cell (?Osteogenic)	Femur	Pain, swelling limitation of motion	R.T., 5,400 r air dose in 21 days	4	0	+	Dead
Belloni and Zanetti[6]	27	Osteogenic	Femur	Weight loss, pain, path. fracture	R.T., 6,000 r	3/12	+	+	Dead
Snapper[81–83]	14	Osteogenic	Femur	?	?	<1	?	+	Dead
Dustin and Ley[23]	13	Osteogenic	Pelvis	Pain, flank mass, dysuria	None	<1	+	+	Dead
Sutro[81]	30	Osteogenic	Tibia	Pain, rapidly enlarging mass	Amputation	3/12	?	?	Alive
Cabitza[9]	39	Chondro-sarcoma	Metatarsal	Increased pain, swelling	Excision	0	?	?	?
Hall, Bersack and Vitolo[33]	37	Fibrosarcoma	Tibia	Pain, swelling	Mid-thigh amputation	0	?	?	?
Perkinson and Higinbotham[67]	22	Osteogenic	Femur	Pain	Disarticulation	8	+	+	Dead
Hobbs, Fischer and Beck[38]	48	Fibrosarcoma	Frontal	Pain, swelling	R.T., tumor dose 4,000 r in 6 wks.	10/12	+	0	Dead
Portis[71]	39	Osteogenic	Scapula, vertebra?	Pain	Interscapular amputation	1	+	+	Dead
Sabanas *et al.*[76]	24	Osteogenic	Maxilla	Swelling, exopthalmos	Surgical exploration	4/12	+	0	Dead
						1/12	0	0	Alive

Hobbs, Fischer and Beck[38]								
Portis[71]	39	Osteogenic	Scapula, vertebra?	Pain	Interscapular amputation	1	+	+	Dead
Sabanas *et al.*[76]	24	Osteogenic	Maxilla	Swelling, exopthalmos	Surgical exploration	4/12	+	0	Dead
Trubnikov[86]	61	Fibrosarcoma	Femur	Pain, swelling, limitation of motion	Amputation	1/12	0	0	Alive
Parrini[65]	8	Osteogenic	Calvarium	Recurrent mass	Radical resection	0	?	?	?
Jaffe[42]	20	Chondrosarcoma	Femur	?	Segmental resection	5	0	0	Alive
Vakhukina[89]	55	Polymorphous osteoblastoclastoma	Left lower leg	Pain, swelling	None	<1	0	+	Dead
Tanner, Dahlin and Childs[86]	18	Osteogenic	Maxilla	Swelling	Radium, ? dose	?2	?	?	Dead
	32	Osteogenic	Mandible	Swelling	R.T. (? dose) hemimandibulectomy	4	0	0	Alive
	24	Fibrosarcoma	Mandible	Swelling, Paresthesias	Resection	1	0	+	Dead
Harris, Dudley and Barry[34]	26	Osteogenic	Femur	Limp	?	4	0	+	Dead
	49	Myxofibrosarcoma	Tibia	Limp	?	2	0	+	Dead
Kieh, DePrez and Harris[48]	42	Osteogenic	Zygoma	Pain, swelling	R.T., (?dose) resection	<1	+	0	Dead
Sethi, Climie and Tuttle[80]	52	Osteogenic	Rib	Pain, cough, dyspnea, weight loss, anorexia	Resection, R.T., air dose 2,000 r	8/12	+	+	Dead
Jager[45]	22	Osteogenic	Maxilla	Swelling	Local resection and R.T. (?dose)	2	+	+	Dead
Schwartz	20	Fibrosarcoma	Mandible	Swelling	R.T. × 2, 2700 r & 1800 r T.D. Multiple local excisions	2	+	0	Dead
	24	Osteogenic	Zygoma	Swelling, spontaneous tooth exfoliation	Repeated resections, regional infusion of methotrexate	1	+	+	Dead

TABLE 3.—POSSIBLE CASES OF MALIGNANT DEGENERATION OF FIBROUS DYSPLASIA

			Fibrous dysplasia		*Sarcoma*		
Year	*Author*	*Sex*	*Age onset*	*Bones affected*	*Age onset*	*Type of sarcoma*	*Bone*	*Course*
1922	Satta[77]	F	10	Humerus	13	Fibrosarcoma	Humerus	No F. U.
1939	Arzeh[2]	F	?	Humerus	14	Osteogenic	Humerus	Alive after 4 yr. F. U.
1953	Hellner[37]	F	12	Iliacs, femurs, tibia	43	Chondrosarcoma (?)	Femur	No F. U.
1956	De Marchi[21]	F	?	Mandible	39	Fibrosarcoma	Mandible	No recurrence during 3 mo. F. U.
	Mogensen[64]	F	19	Femur,* tibia, rib, radius, mandible, orbit, toe	36	(No histology)	Orbit (?)	Died less than 1 year after clinical diag. of sarcoma

* Case of Albright's syndrome; R.T. (? dose) given to fib. dysp.

TABLE 4.—AGE AND SEX I

Osteogenic sarcoma after fibrous dysplasia

Fibrosarcomas after fibrous dysplasia

Sarcomas after monostotic fibrous dysplasia

Sarcomas after polyostotic fibrous dysplasia

Sarcomas after both monostotic and polyostotic fibrous dysplasia

Fig. 6.—Th

TABLE 4.--AGE AND SEX INCIDENCE OF 28 PATIENTS WITH SARCOMAS SECONDARY TO FIBROUS DYSPLASIA

	No. of patients	*Mean age of patient at onset in years*		*Mean lag in years*	*% Female*
		Fibrous Dysplasia	*Bone Sarcoma*		
Osteogenic sarcoma after fibrous dysplasia	19	14	30	12	53
Fibrosarcomas after fibrous dysplasia	7	21	40	18	28
Sarcomas after monostotic fibrous dysplasia	14	17	34	15	29
Sarcomas after polyostotic fibrous dysplasia	14	15	29	11.5	64
Sarcomas after both monostotic and polyostotic fibrous dysplasia	28	16	32	13.5	50

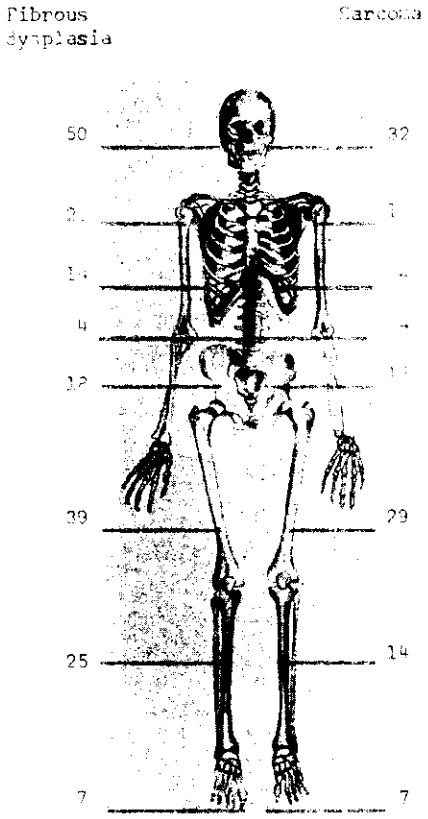

Fig. 6.—The skeletal localization in per cent of fibrous dysplasia and its secondary sarcomas in 28 patients.

mon site in the monostotic form was the facial bones or skull (50%), while the most frequent site of involvement in the polyostotic variety was the femur (62%), with the cranio-facial, humerus, pelvis, tibia and fibula in descending order.

PATHOLOGY. The histopathology of the fibrous dysplasia in these 28 cases did not differ in any significant way from the usual pattern of fibrous dysplasia. Similarly, the pathology of the sarcomas which developed was not different from the sarcomas arising in normal bones. In our second case the initial pathological diagnosis of a fibrosarcoma was changed to an osteogenic sarcoma when the necropsy showed pulmonary metastases forming osteoid and bone. In several instances the histopathologic evaluation of the biopsy specimen has been in error, with both false positives (Belloni and Zanetti[6]) and false negatives (Fromme[29]). The clinical and Roentgen features must, therefore, be considered before carrying out ablative surgery. In one case, for example, the pathologist (Haunfelder[35]) made the diagnosis of osteogenic sarcoma secondary to fibrous dysplasia, but the patient was living and well 9 years later without definitive therapy.

In two published cases (Coley and Stewart[14], Perkinson and Higinbotham[67]) and in one personal case the serum alkaline phosphatase became elevated at the onset of the sarcoma.

PROGNOSIS OF THE SARCOMA. In Jaffe's experience[43] of the sarcomas arising in an area of fibrous dysplasia, the fibrosarcomas had a better prognosis than did the osteogenic variety. However, in our collected series of 18 osteogenic sarcomas and 4 fibrosarcomas (where the follow-up was adequate), the 2-year survival rate was the same in both tumors (50%). The 5-year survival rate for both was less than 20%. Whether the fibrous dysplasia was monostotic or polyostotic made no difference in the subsequent survival. The rate of metastasis was, however, greater (90%) in cases developing after polyostotic fibrous dysplasia than after monostotic fibrous dysplasia (50%). (This difference was statistically significant, $P < 0.01$.)

A COMPARISON OF THE 28 SECONDARY SARCOMAS WITH *de novo* BONE SARCOMAS. We compared the clinical features of the sarcomas engrafted on fibrous dysplasia with those of *de novo* bone sarcomas. In our collected series we did not observe the expected 3:1 female to male ratio that has been noted in the general population of fibrous dysplasia patients. Instead the ratio was 1:1, indicating the higher frequency of sarcomatous degeneration in males. Similarly, males predominate among patients with *de novo* bone sarcomas (Coley[13], Dahlin[19], Gilmore and McKeon[30]). The symptomatology and the radiological appearance of the sarcomas were similar. The age of onset of the sarcoma was the same as that of sarcomas in the general population, both for osteogenic (Dahlin[19], Hohmann, Hackenbroch and Lindemann[39]) and for fibrosarcomas (Gilmore and McKeon[30]). The 5-year survival rate of patients with osteogenic sarcoma secondary to fibrous dysplasia was 14%, virtually the same as the 5-year survival rate of osteogenic sarcoma in the general population (Coley[13], Coventry and Dahlin[16], Lindbom, Gunnar and Spjut[57]).

The skeletal distribution of the sarcomatous lesions reflected the distribution of fibrous dysplasia rather than the distribution of the *de novo* sarcomas (Table 5). For example, osteogenic and fibrosarcoma of bone are rare in the cranio-facial regions (Gilmore and McKeon[30], Price[73]), while sarcomas associated with fibrous dysplasia are most common in this anatomic site. This difference was also noted in 7 cases of fibrosarcoma which occurred with fibrous dysplasia, where 4 were situated in the cranio-facial region. *De novo* fibrosarcomas in the

general population, however, are most common in the femur, tibia and fibula (Gilmore and McKeon[30]). Similarly, osteogenic sarcomas associated with fibrous dysplasia occurred in the cranio-facial region in 32% of the cases. The symptoms, signs, radiologic appearance and pathologic findings of the sarcomas in these 28 patients did not differ significantly from those of patients with *de novo* sarcomas.

patients among 82,000 Roentgen-ray examinations. Since 1,522,000 Roentgen-ray examinations were carried out from 1940 through 1961, a total of 427 patients with fibrous dysplasia was obtained. The Roentgen-ray records, therefore, showed an incidence of malignant degeneration of 2:427 or 0.5%.

As our second method of estimating this incidence we used the total number of reported cases of both fibrous

TABLE 5.--THE SKELETAL LOCALIZATION OF FIBROUS DYSPLASIA AND ITS SECONDARY SARCOMAS IN 28 PATIENTS

Site	*% of patients with fibrous dysplasia and sarcoma*		*% of patients with de novo osteogenic sarcomas*[73]
	Fibrous Dysplasia	*Sarcoma*	
Cranio-facial	50	32	7.5
Ribs	14	4	5
Humerus and Shoulder	21	11	11
Vertebrae	4	4	1
Elbow	0	0	1
Pelvis	18	4	13
Femur	39	29	36
Tibia and Fibula	25	14	18
Foot	7	7	1
Cases	28	28	36

INCIDENCE OF MALIGNANT DEGENERATION OF FIBROUS DYSPLASIA. Parrini[65] has stated that 3% of patients with Albright's syndrome develop a bone sarcoma. We were interested in making an independent estimate of this statistic, and we approached this problem by a study of two sources of data, the Presbyterian Hospital Radiology Department and our review of the literature.

During the 22-year period from January, 1940, through December, 1961, there were 2 cases of malignant degeneration of fibrous dysplasia at the Columbia-Presbyterian Medical Center. The Presbyterian Hospital, Harkness Pavilion and the Neurologic Institute records for the 12 months of 1961 were used as a representative sample of the roentgenologically-detected frequency of fibrous dysplasia over the 22-year period. In 1961, the radiological diagnosis of fibrous dysplasia was made in 23

dysplasia and secondary sarcomas. We started with the published cases of McCune-Albright's syndrome[1,63], where the efficiency of publishing the clinically observed cases would be the highest. By 1951, Pritchard[75] was able to collect 37 cases of polyostotic fibrous dysplasia with precocious puberty. According to Jaffe[43] and Schlumberger[78] there are 40 cases of monostotic fibrous dysplasia for every case of Albright's syndrome. This gave us a product of 1,480 cases of monostotic fibrous dysplasia, and adding the 37 cases of polyostotic fibrous dysplasia we obtained a total of 1,517. Six cases of malignant degeneration of fibrous dysplasia were published between 1939 and 1951. Therefore, the estimated incidence of malignant degeneration from this published data is 6:1517 or 0.4%.

Returning to Parrini's statistic, our

review of the literature disclosed approximately 100 cases of Albright's syndrome, of which 4 underwent malignant change.

FREQUENCY OF MALIGNANT CHANGE IN NORMAL BONES AND IN OTHER BENIGN BONE TUMORS. Since the incidence of bone sarcomas in the general population is 0.001% (Coley[13]), fibrous dysplasia undergoes malignant change at 400 times the spontaneous rate.

When we consider other benign bone lesions with a malignant potential, we find that the rate of sarcomatous degeneration is higher among patients where many bones are affected. In Ollier's disease approximately 30% of the patients eventually develop a malignancy (Coley[13]), while solitary enchondromas nearly always remain benign. Malignancy develops in 2% of all patients with Paget's disease (Goldenberger[31]), but in 10 to 25% of florid cases. Eleven per cent of patients with hereditary multiple exostoses develop a chondrosarcoma (Coley[13]), while patients with solitary osteochondromas rarely experience malignant change. It is not surprising, therefore, to find that polyostotic fibrous dysplasia has a higher rate of malignant change than monostotic fibrous dysplasia. In our collected series of 28 patients, half had the polyostotic form, a ratio greatly in excess of that present in the general fibrous dysplasia population (Coley[13], Schlumberger[78]).

To account for the greater rate of malignant change and for the greater rate of metastasis, one might cite Harris, Dudley and Barry's[34] finding of a more primitive bone in polyostotic fibrous dysplasia (less lamellation seen with polarized light). This is analagous to Ollier's disease, where the cartilage is histologically less mature in multiple enchondromas than in solitary enchondromas.

TABLE 6.—PROGNOSIS OF 22 PATIENTS WITH SARCOMAS SECONDARY TO FIBROUS DYSPLASIA

	No. of patients with adequate follow-up	*% of patients with metastases*	*Survival rate (%)*	
			2 years	*5 years*
Osteogenic sarcomas after fibrous dysplasia	17	80	41	13
Fibrosarcomas after fibrous dysplasia	4	50	50	0
Sarcomas after monostotic fibrous dysplasia	12	50	42	9
Sarcomas after polyostotic fibrous dysplasia	10	90	50	20
Sarcomas after both monostotic and polyostotic fibrous dysplasia	22	68	45	14
Osteogenic[13,16,57,73] sarcomas in general population	1,542	56		15
Fibrosarcomas of bone in general population[30,73]	58		35	30

THE ROLE OF RADIATION IN THE PATHOGENESIS OF SARCOMAS SECONDARY TO FIBROUS DYSPLASIA. Since several authors have doubted the causal relationship between bone sarcoma and pre-existing fibrous dysplasia, we should give evidence for this etiological association. It is noteworthy that in this series of 28 patients, sarcomas always developed in bones affected by fibrous dysplasia, and never in a normal bone. It has been claimed that the radiation given to the fibrous dysplasia is exclusively responsible for the malignant change. To re-

fute this concept, we can cite the fact that 16 patients had no radiotherapy at all.

That radiation can induce bone sarcomas in man was first documented by Martland, when he reported their development in luminous dial painters who had ingested radium (Aub *et al.*[3], Martland and Humphries[3,62]). This causal relationship has been well established experimentally (Ely *et al.*[25], Finarty *et al.*[27], Loomey *et al.*[58]). Although the usual latent period before the development of the sarcoma in clinical cases is 14 years (Bloch[7]), latent periods as short as 3 years (Cohen and D'Angio[12]) and as long as 37 years have been reported (Woodard and Higinbotham[91]). While some cases of bone sarcoma occurring after doses as low as 1,000r have been reported (Cohen and D'Angio[12], Cruz, Coley and Stewart[17]), it is generally stated that 3,000r are required to produce an osteogenic sarcoma (Cahan *et al.*[10], Jones[46]). As with other radiation effects (erythema, growth retardation, necrosis), the duration of the course of treatment must be considered along with the total dose (Finkel, Bergstrand and Biskis[28], Macpherson, Owen and Vaughan[60]). Unfortunately, the time-dose relationship in radiation-induced tumors in man has not been adequately explored.

Of the 11 patients in this series who received radiotherapy prior to the sarcoma, we have adequate data regarding the dose in 9. In 4 of the 9 the total dose was less than 3,000r, and in view of the discussion above, this amount of radiation may have been insufficient to account for the malignant transformation. Eliminating these 4 cases results in an incidence of post-radiation sarcoma of less than 20% in this collected series. The average lag period between the last course of radiotherapy and the onset of the sarcoma in the 5 patients who had received an adequate dose was 11 years. This is in contrast to the average lag period of 14 years in sarcomas arising in irradiated normal bone. Sixteen patients had no radiotherapy at all. However, the fact that 11 patients did receive some radiotherapy would raise the question that the ionizing radiation enhanced the natural tendency of fibrous dysplasia to undergo sarcomatous change. For that reason, even though it is still prescribed (Portmann[72]), radiotherapy of fibrous dysplasia is not advised.

OTHER NEOPLASMS ASSOCIATED WITH FIBROUS DYSPLASIA. Two other tumors have been observed in patients with fibrous dysplasia. One neoplasm, the adamantinoma, has been noted in 9 patients (Baker, Dockerty and Coventry[4], Cohen, Dahlin and Pugh[11]), and the other neoplasm, the cutaneous fibromyxoma, has been reported in 4 cases (Braunwarth[8], Heinemann and Worth[36], Lick and Viehweger[56], Uehlinger[88]).

MANAGEMENT OF PATIENTS WITH FIBROUS DYSPLASIA. If the fibrous dysplasia lesion is asymptomatic, treatment is not justified. If a pathologic fracture of the femur or tibia is apt to occur, curettage with implantation of bone chips should be considered. With large osseous defects, bank bone may be used. For a coxa vara an osteotomy is recommended (Hohmann, Hackenbroch and Lindemann[39]). When possible, it is best to withhold operative intervention until after puberty, as the recurrence rate is less in the mature patient. Cosmetic considerations will be important in the management of localized deformities of the skull and facial bones. Radiotherapy for fibrous dysplasia is not recommended since we have found 5 cases of malignant transformation after a minimum tumor dose of 3,000r. Furthermore, its salutary effect on fibrous dysplasia has not been established. In a patient with fibrous dysplasia, the physician must be alert to symptoms of malignant change, such as pain and rapid enlargement of the lesion. On the roentgenograms, the extensive alterations due to the fibrous dysplasia lesion (especially after surgi-

cal intervention) may hinder early detection of a sarcoma. Suspicious clinical findings therefore make a biopsy mandatory, and follow-up radiographs are indicated.

The treatment of sarcomas arising in fibrous dysplasia is the same as that of the *de novo* bone sarcomas. If it occurs in the skull, a local resection should be done where possible. In the mandible, a hemimandibulectomy (Schwartz and Alpert[79]) is indicated. When it occurs in an extremity, disarticulation of the affected bone is the accepted approach (Coley[13]). In the rib a wide resection is recommended. Postoperative radiotherapy has not proved to be of value in sarcoma after fibrous dysplasia (Hohmann, Hackenbroch and Lindemann[39]).

Summary. The authors have analyzed the published data in 26 well-documented cases of sarcomas secondary to fibrous dysplasia, with 2 additional cases from the Presbyterian Hospital. In 5 instances sufficient Roentgen-irradiation had been given to possibly contribute to the development of the sarcoma. Sixteen patients had received no radiation at all.

The incidence of malignant degeneration of fibrous dysplasia was estimated to be 1:200, or about ¼ the incidence of malignant degeneration in Paget's disease. Sarcomas occurred more often in polyostotic fibrous dysplasia than in the monostotic form. There was a higher frequency of malignant change in males affected by fibrous dysplasia. The onset of the sarcoma occurred at a mean age of 32 years, with a mean lag of 13.5 years after the onset of the fibrous dysplasia. The most important findings heralding the malignant transformation were pain, swelling and a significant change in the Roentgen appearance. The cranio-facial region was the most common site of these sarcomas. The osteogenic sarcoma was the predominant histologic type.

The treatment of these secondary sarcomas is the same as that of *de novo* sarcomas. Fourteen per cent of the patients with sarcomas survived 5 years.

ACKNOWLEDGMENT: The authors are indebted to Drs. P. Carbonara and L. Finkelstein for their aid in translating articles.

REFERENCES

1. **Albright, F., Butler, A. M., Hampton, A. O.,** and **Smith, P. A.:** New England J. Med., **216**, 727, 1937.
2. **Arzela, I.:** Chir. Org. Mov., **24**, 197, 1939.
3. **Aub, J. C., Evans, R. D., Hempelman, L. H.,** and **Martland, H. S.:** Medicine, **31**, 221, 1952.
4. **Baker, P. L., Dockerty, M. B.,** and **Coventry, M. B.:** J. Bone and Joint Surg., **36A**, 704, 1954.
5. **Belloni, L.:** Arch. Ort., **59**, 414, 1946.
6. **Belloni, L.,** and **Zanetti, E.:** La Ricerca Scientifica, **19**, 1317, 1949.
7. **Bloch, C.:** Am. J. Roentgenol., Rad. Therapy, & Nuclear Med., **87**, 1157, 1962.
8. **Braunwarth, K.:** Fortschr. a. d. Geb. d Roentgenstrahlen, **78**, 589, 1953.
9. **Cabitza, A.:** Chir. Org. Mov., **36**, 8, 1951.
10. **Cahan, W. G., Woodard, H. O., Higinbotham, N. L., Stewart, F. W.,** and **Coley, B. L.:** Cancer, **1**, 3, 1948.
11. **Cohen, D. M., Dahlin, D. C.,** and **Pugh, D. G.:** Ibid., **15**, 515, 1962.
12. **Cohen, J.,** and **D'Angio, G. J.:** Am. J. Roentgenol., Rad. Therapy, & Nuclear Med., **36**, 502, 1961.
13. **Coley, B. L.:** Neoplasms of Bone. New York: Paul B. Hoeber, p. 270, 1960.
14. **Coley, B. L.,** and **Stewart, F. W.:** Ann. Surg., **121**, 872, 1945.
15. **Cottone, D.:** Rad. Prat., **6**, 82, 1956.
16. **Coventry, M. B.,** and **Dahlin, D. C.:** J. Bone and Joint Surg., **39A**, 741, 1957.
17. **Cruz, M., Coley, B. L.,** and **Stewart, F. W.:** Cancer, **10**, 72, 1957.
18. **Dahlin, D. C.:** Bone Tumors. Springfield: Charles C Thomas, p. 13, 1957.
19. Idem: Ibid., p. 129.

20. **Daves, M. L.,** and **Yar**
21. **De Marchi, R.:** Friul
22. **Dunlap, C. E., Aub, J.**
23. **Dustin, R.,** and **Ley,**
24. **Elmslie, B.:** Brit. J. S
25. **Ely, J. O., Ross, M. H.,** *In* **Blair, H.A.** (e Hill Book Co., p.
26. **Ferrero, C.:** Presse M
27. **Finarty, J. C., Binhan** Proc., **13**, 43, 195
28. **Finkel, M., Bergstrand**
29. **Fromme, L.:** Arch. K
30. **Gilmore, W. S., Jr.,** an
31. **Goldenberger, R. R.:**
32. **Haberer, H.:** Arch. f
33. **Hall, A., Bersack, S. R**
34. **Harris, W. H., Dudley**
35. **Haunfelder, D.:** Deu
36. **Heinemann, G.,** and **V**
37. **Hellner, H.:** Arch. k
38. **Hobbs, H. A., Jr., Fis**
39. **Hohmann, G., Hacke** Stuttgart: Georg
40. **Jaffe, H.:** Bull. New
41. Idem: J. Mt. Sinai
42. Idem: Tumors and Febiger, p. 134,
43. Idem: Ibid., p. 266.
44. Idem: Ibid., p. 304.
45. **Jager, M.:** Zentralbl.
46. **Jones, A.:** Brit. J. R
47. **Katz, J. F.:** J. Mt. S
48. **Kieh, C. L., De Prez,**
49. **Kienbock, R.:** Diffe Wien: Urban u
50. **Knaggs, R. L.:** Brit.
51. **Koletsky, S.,** and **Gust**
52. **Kragh, L. V., Dahlin,**
53. **Leeds, N.,** and **Seam**
54. **Lichtenstein, L.:** Arc
55. **Lichtenstein, L.,** and
56. **Lick, R. F.,** and **Vieh** medizin, **97**, 33,
57. **Lindbom, A., Gunnar,**
58. **Loomey, W. B., Hast** **73**, 1006, 1955.
59. **Marie, P., Clunet, J.,**
60. **Macpherson, S., Owe**
61. **Martens:** Klin. Wch
62. **Martland, H. S.,** and
63. **McCune, D. I.,** and
64. **Mogensen, E. F.:**
65. **Parrini, L.:** Chirurg
66. **Parisel, C.:** Bull. et
67. **Perkinson, N. G.,** an
68. **Pick, L.:** Klin. Wch
69. **Pisanni, A.,** and **Cap**
70. **Platt, H.:** Brit. J. S
71. **Portis, R. B.:** Bull.
72. **Portmann, U. V.** (e p. 494, 1950.
73. **Price, C. H. G.:** Br

20. **Daves, M. L.**, and **Yardley, J. H.**: Am. J. Med. Sci., **234**, 590, 1957.
21. **De Marchi, R.**: Friuli Medico, **11**, 639, 1956.
22. **Dunlap, C. E., Aub, J. C., Evans, R. D.**, and **Harris, R. S.**: Am. J. Path., **20**, 1, 1944.
23. **Dustin, R.**, and **Ley, R. A.**: Rev. Belge. Path., **20**, 52, 1950.
24. **Elmslie, B.**: Brit. J. Surg., **2**, 17, 1914.
25. **Ely, J. O., Ross, M. H., Metcalf, R. G., India, F. A., Barnett, T. B.**, and **Casarett, G. W.**: *In* **Blair, H.A.** (ed.), Biological Effects of External Radiation. New York: McGraw-Hill Book Co., p. 419, 1954.
26. **Ferrero, C.**: Presse Med., **55**, 142, 1947.
27. **Finarty, J. C., Binhammer, R. T., Schneider, M.**, and **Cunningham, A. W. B.**: Fed. Proc., **13**, 43, 1954.
28. **Finkel, M., Bergstrand, P.**, and **Biskis, B.**: Radiology, **77**, 269, 1961.
29. **Fromme, L.**: Arch. Klin. Chir., **152**, 601, 1928.
30. **Gilmore, W. S., Jr.**, and **McKeon, G. D.**: J. Bone & Joint Surg., **40A**, 121, 1958.
31. **Goldenberger, R. R.**: Bull. Hosp. Joint Dis., **22**, 1, 1961.
32. **Haberer, H.**: Arch. f. klin. Chir., **82**, 873, 1907.
33. **Hall, A., Bersack, S. R.**, and **Vitolo, R. E.**: J. Bone & Joint Surg., **37A**, 1019, 1955.
34. **Harris, W. H., Dudley, R. H.**, and **Barry, R. J.**: Ibid., **44A**, 207, 1962.
35. **Haunfelder, D.**: Deutsche Zahnaerztl. Ztschr., **14**, 1399, 1959.
36. **Heinemann, G.**, and **Worth, D.**: Beitr. klin. Chir., **197**, 327, 1958.
37. **Hellner, H.**: Arch. klin. Chir., **277**, 160, 1953.
38. **Hobbs, H. A., Jr., Fischer, W. C.**, and **Beck, R. E.**: Am. J. Roentgenol., **76**, 320, 1956.
39. **Hohmann, G., Hackenbroch, M., Lindemann**: Handbuch der Orthopaedie, Volume I, Stuttgart: Georg Thieme, p. 259, 1957.
40. **Jaffe, H.**: Bull. New York Acad. Med., **22**, 588, 1946.
41. Idem: J. Mt. Sinai Hosp., **12**, 364, 1946.
42. Idem: Tumors and Tumorous Conditions of Bone and Joints. Philadelphia: Lea & Febiger, p. 134, 1958.
43. Idem: Ibid., p. 266.
44. Idem: Ibid., p. 304.
45. **Jager, M.**: Zentralbl. allg. Path., **103**, 291, 1962.
46. **Jones, A.**: Brit. J. Radiol., **26**, 273, 1953.
47. **Katz, J. F.**: J. Mt. Sinai Hosp., **17**, 187, 1950.
48. **Kieh, C. L., De Prez, J. D.**, and **Harris, A. H.**: Am. J. Surg., **102**, 835, 1962.
49. **Kienbock, R.**: Differentialdiagnose der geschwulstigen Knochenkrankenheiten, Berlin-Wien: Urban und Schwarzenberg, p. 55, 1933.
50. **Knaggs, R. L.**: Brit. J. Surg., **11**, 347, 1923-1924.
51. **Koletsky, S.**, and **Gustafson, G. E.**: Am. J. Path., **29**, 606, 1953.
52. **Kragh, L. V., Dahlin, D. C.**, and **Erich, J. B.**: Am. J. Surg., **96**, 496, 1958.
53. **Leeds, N.**, and **Seaman, W. B.**: Radiology, **78**, 570, 1962.
54. **Lichtenstein, L.**: Arch. Surg., **36**, 874, 1938.
55. **Lichtenstein, L.**, and **Jaffe, H.**: Arch. Path., **33**, 777, 1942.
56. **Lick, R. F.**, and **Viehweger, G.**: Fortschr. a. d. Geb. d. Roentgenstrahlen u.d. Nuklearmedizin, **97**, 33, 1962.
57. **Lindbom, A., Gunnar, S.**, and **Spjut, H.**: Acta radiol., **56**, 1, 1956.
58. **Loomey, W. B., Hasterlick, R. J., Brues, A. M.**, and **Skirmont, E.**: Am. J. Roentgenol., **73**, 1006, 1955.
59. **Marie, P., Clunet, J.**, and **Raulot-LaPointe, G.**: Bull. Ass. fr. cancer, 3, 404, 1910.
60. **Macpherson, S., Owen, M.**, and **Vaughan, J.**: Brit. J. Radiol., **35**, 221, 1962.
61. **Martens:** Klin. Wchnschr., **5**, 528, 1926.
62. **Martland, H. S.**, and **Humphries, R. E.**: Arch. Path., **7**, 406, 1929.
63. **McCune, D. I.**, and **Bruch, H.**: Am. J. Dis. Child., **54**, 806, 1937.
64. **Mogensen, E. F.**: Acta med. Scandinav., **161**, 453, 1958.
65. **Parrini, L.**: Chirurgia, **12**, 3, 1957.
66. **Parisel, C.**: Bull. et mem. Soc. Belg. Orthop., **4**, 6, 1962.
67. **Perkinson, N. G.**, and **Higinbotham, N.**: Cancer, **8**, 396, 1955.
68. **Pick, L.**: Klin. Wchnschr., **5**, 959, 1926.
69. **Pisanni, A.**, and **Caprotti, M.**: Ann. Radiol. diag., **30**, 173, 1962.
70. **Platt, H.**: Brit. J. Surg., **34**, 232, 1946.
71. **Portis, R. B.**: Bull. Hosp. Joint. Dis., **17**, 305, 1956.
72. **Portmann, U. V.** (ed.): Clinical Therapeutic Radiology. New York: Thomas Nelson, p. 494, 1950.
73. **Price, C. H. G.**: Brit. J. Cancer, **6**, 46, 1952.

74. Idem: Ibid., **9**, 558, 1955.
75. **Pritchard, J. E.:** Am. J. Med. Sci., **222**, 313, 1951.
76. **Sabanas, A. O., Dahlin, D. C., Childs, D. S.,** and **Ivins, J. C.:** Cancer, 9, 528, 1956.
77. **Satta, F.:** Arch. Ortop., **38**, 3, 1922.
78. **Schlumberger, H. G.:** Mil. Surg., **99**, 504, 1946.
79. **Schwartz, D. T.,** and **Alpert, M.:** Oral Surg., Oral Med. & Oral Path., **16**, 769, 1963.
80. **Sethi, R. S., Climie, A. R. W.,** and **Tuttle, W. M.:** J. Bone and Joint Surg., **44A**, 183, 1962.
81. **Snapper, I.:** Chin. Med. J., **56**, 303, 1939.
82. Idem: Medical Clinic on Bone Disease, A Text and Atlas, 2nd ed. London: Interscience Publishers, Inc., p. 202, 1949.
83. **Snapper, I.,** and **Parisel, C.:** Quart. J. Med., **2**, 407, 1933.
84. **Sutro, C. J.:** Bull. Hosp. Joint Dis., **12**, 217, 1951.
85. **Tanner, H. C., Dahlin, D. C.,** and **Childs, D. S.:** Oral Surg., Oral Med., & Oral Path., **14**, 837, 1961.
86. **Trubnikov, V. F.:** Ortop. Trav., protez., **17**, 53, 1956.
87. **Uehlinger, F.:** Virchow's Arch. Path. Anat., **306**, 255, 1940.
88. Idem: Fortschr. a. d. Geb. d. Roentgenstrahlen, **64**, 41, 1941.
89. **Vakhurkina, A. M.:** Arkh. Pat., Moskva, **20**, 18, 1958.
90. **Wanke, R.:** Deutsche Ztschr. Chir., **201**, 358, 1927.
91. **Woodard, H. O.,** and **Higinbotham, N. L.:** Am. J. Med., **32**, 96, 1962.

SUMMARIO IN INTERLINGUA

Transformation Maligne de Dysplasia Fibrose

Le autores ha analysate le publicate datos in 26 ben-documentate casos de sarcoma secundari a dysplasia fibrose e ha addite datos ab 2 casos additional vidite al Hospital Presbyterian de New York. In 5 casos le grado de roengeno-irradiation usate in le therapia esseva sufficiente pro possibilemente explicar in parte le disveloppamento del sarcoma. Dece-sex patientes habeva recipite nulle irradiation del toto.

Esseva estimate que le incidentia de degeneration maligne de dysplasia fibrose es 1:200, i.e., un quarto del incidentia de degeneration maligne in morbo de Paget. Sarcoma esseva plus frequente in le forma polyostotic de dysplasia fibrose que in le forma monostotic. Esseva notate un plus alte frequentia de alteration maligne in masculos con dysplasia fibrose que in femininas. Le declaration del sarcoma occurreva a un etate medie de 32 annos, con un intervallo medie de 13,5 annos post le declaration del dysplasia fibrose. Le plus importante constatationes annunciante le maligne transformation esseva dolor, tumescentia, e un significative alteration in le apparentia roentgenographic. Le region cranio-facial esseva le sito le plus commun de iste sarcomas. Le predominante typo histologic esseva sarcoma osteogene.

Le tractamento de tal sarcomas secundari non differe ab le tractamento de sarcomas primari. Dece-quatro pro cento del patientes con sarcomas superviveva 5 annos.